Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal rTMS in major depression

Anhedonia and Reward-Circuit Connectivity Distinguish Nonresponders from Responders to Dorsomedial Prefrontal Repetitive Transcranial Magnetic Stimulation in Major Depression

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Background: Depression is a heterogeneous mental illness. Neurostimulation treatments, by targeting specific nodes within the brain's emotion-regulation network, may be useful both as therapies and as probes for identifying clinically relevant depression subtypes.

Methods: Here, we applied 20 sessions of magnetic resonance imaging-guided repetitive transcranial magnetic stimulation (rTMS) to the dorsomedial prefrontal cortex in 47 unipolar or bipolar patients with a medication-resistant major depressive episode.

Results: Treatment response was strongly bimodal, with individual patients showing either minimal or marked improvement. Compared with responders, nonresponders showed markedly higher baseline anhedonia symptomatology (including pessimism, loss of pleasure, and loss of interest in previously enjoyed activities) on item-by-item examination of Beck Depression Inventory-II and Quick Inventory of Depressive Symptomatology ratings. Congruently, on baseline functional magnetic resonance imaging, nonresponders showed significantly lower connectivity through a classical reward pathway comprising ventral tegmental area, striatum, and a region in ventromedial prefrontal cortex. Responders and nonresponders also showed opposite patterns of hemispheric lateralization in the connectivity of dorsomedial and dorsolateral regions to this same ventromedial region.

Conclusions: The results suggest distinct depression subtypes, one with preserved hedonic function and responsive to dorsomedial rTMS and another with disrupted hedonic function, abnormally lateralized connectivity through ventromedial prefrontal cortex, and unresponsive to dorsomedial rTMS. Future research directly comparing the effects of rTMS at different targets, guided by neuroimaging and clinical presentation, may clarify whether hedonia/reward circuit integrity is a reliable marker for optimizing rTMS target selection.

Key Words: Anhedonia, betweenness, depression, dorsomedial, fMRI, graph theory, prefrontal, rTMS, stimulation, subtype

Major depression is heterogeneous in its course, symptomatology, and responsiveness to treatment. A variety of clinical features or biomarkers have been proposed to reliably parse this heterogeneity into subtypes useful for prognosis or treatment selection. Examples include Leonhard's (1) original distinction between unipolar and bipolar illness, as well as later proposed distinctions between melancholic and atypical depression (2), responsiveness to the dexamethasone suppression test (3), and the presence of agitation or mixed features (4). However, the utility of most such clinical features in guiding treatment selection remains controversial.

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Anhedonia is a core symptom of depression in the DSM-IV diagnostic criteria and is drawing increasing attention as a key feature of the illness (5,6). Overall, studies using behavioral, pharmacologic, and neuroimaging methods suggest a disruption of the appetitive and consummatory aspects of reward in depression (7–11). However, its potential relevance to treatment selection and outcome prediction has received relatively little attention to date.

Current neuroimaging-based models of depression posit network-level changes in the interactions between emotion-regulating regions, including dorsomedial prefrontal cortex (DMPFC) and ventromedial prefrontal cortex (VMPFC), dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex, and dorsal and ventral anterior cingulate cortex (ACC), as well as amygdala, hippocampus, and brainstem monoaminergic nuclei (12–17). The implications of this model are twofold: first, that different clinical subtypes of depressive illness could arise from different patterns of network disruption, and second, that different treatment modalities could target this network at different points, thus addressing specific subtypes of illness.

Neuromodulation techniques, such as deep brain stimulation (DBS) or repetitive transcranial magnetic stimulation (rTMS), are neuroanatomically specific in their effects on brain activity. Any putative network-level subtypes of depression might therefore be most readily apparent with these treatment modalities. Deep brain stimulation and rTMS may therefore be useful not only as therapies but also as tools for parsing the heterogeneity of depression in ways that are intrinsically relevant to treatment selection.

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In depression, the conventional rTMS target is the DLPFC (18,19). However, convergent evidence from lesion, stimulation, and neuroimaging studies (20) suggests that the DMPFC may also play a central role in depression. Dorsomedial prefrontal cortex lesions confer a strong risk of depressive symptoms (21,22). Inadvertent deactivation of DMPFC via DBS can precipitate immediate depressive symptomatology (23). The DMPFC also shows consistent gray matter reduction in volumetric studies of depression (24). Resting-state functional magnetic resonance imaging (fMRI) studies have characterized the DMPFC as a dorsal nexus region where networks for cognitive control, default-mode rumination, and somatic marker generation converge in depressed patients but not healthy control subjects (16). The DMPFC may therefore present a promising target for excitatory rTMS in depression (20), as suggested by a recent case report (25).

Aside from the dorsal nexus, other regions could potentially contribute to the heterogeneity of depression. The mathematical tools of graph theory, which enables detailed analysis of complex network topology (26), are now being used to identify pathologic patterns of brain activity in Alzheimer dementia, schizophrenia, autism, and mood disorders (27–30). A particular network parameter, known as betweenness centrality (BC), measures the number of shortest paths between all other points A and B that pass through a given node. Nodes with high BC act as chokepoints that can be particularly damaging to network traffic if they are disrupted.

Betweenness centrality maps have been used to identify vulnerable points in energy transmission networks (31), critical proteins in biochemical pathways for therapeutic targeting in neurodegenerative disease (32,33), and abnormal patterns of whole-brain functional connectivity in Alzheimer dementia (34). Betweenness centrality has also recently been applied to resting-state fMRI series to distinguish patients with depression from healthy control subjects (35). However, to our knowledge, this approach has never previously been used to distinguish responders from nonresponders to a given treatment.

In the present study, we first sought to employ DMPFC-rTMS as a probe, as well as a treatment, to test the hypothesis that this intervention would reveal discrete subtypes of patients (as opposed to a unimodal continuum of response) within a heterogeneous sample of patients with treatment-refractory depression. Since virtually no studies of DMPFC-rTMS have been performed to date, we then adopted a more descriptive approach, examining pretreatment clinical and fMRI data to characterize the subtypes in greater detail, both in terms of symptomatology and BC maps of brain activity. Finally, we assessed the congruency of the clinical-symptom outcome predictors with the neural activity outcome predictors.

Methods and Materials

Design Overview

This study investigated the effects of 20 sessions of open-label, add-on bilateral magnetic resonance imaging (MRI)-guided rTMS of the DMPFC in a series of patients meeting DSM-IV criteria for unipolar or bipolar disorder and a current major depressive episode resistant to medication. Following initial clinical assessment, patients underwent MRI and a baseline symptom assessment before motor threshold testing, then began treatment 3 days later. During treatment, patients completed daily self-assessment questionnaires and weekly clinician-rated assessments as described below. Patients achieving response but not remission criteria were offered an additional 10 sessions (2 weeks) of treatment. Patients then underwent clinical assessments at 2, 4, 6, 12, and 26 weeks posttreatment to assess clinical response. Supplement 1 provides a more detailed description of all methods used.

Subjects

Subjects were a series of 47 consecutive patients (20 male patients, 27 female patients, age 42.2 ± 12.7 years), with either unipolar ($n = 38$) or bipolar ($n = 9$) illness referred to the University Health Network's MRI-Guided rTMS Clinic for the treatment of a major depressive episode. All patients had a clinical history of resistance to at least two adequate medication trials (discontinuation of a medication trial due to adverse effects also being included in this count), including at least one trial in the current episode. Baseline symptom severity was a mean 22.7 ± SD 6.8 on the 17-item Hamilton Rating Scale for Depression (HAMD-17) and 32.6 ± SD 10.6 on the Beck Depression Inventory-II (BDI-II). Major depressive episode duration was a mean 40.6 months ± SD 55.7. The total number of previous medication trials (including antidepressants and add-on mood stabilizers, antipsychotics, or psychostimulants, discontinued due to either intolerance or inefficacy) ranged from 2 to 25 (mean 6.7 ± SD 4.3). Seven patients had also previously failed to respond to electroconvulsive therapy.

Regarding exclusion criteria, no patients with active substance use or psychotic disorders participated in the study. Patients with potential contraindications to rTMS or MRI, including a history of seizures, implanted devices, foreign metal bodies, cardiac arrhythmia, unstable medical conditions, or pregnancy, were excluded from treatment. All patients had maintained a stable regimen of medications for ≥4 weeks before treatment, with no changes throughout the course of treatment. All patients provided informed consent to treatment, and the study was approved by the Research Ethics Board of the University Health Network.

rTMS Treatment Parameters

Repetitive transcranial magnetic stimulation was delivered using a MagPro R30 rTMS device (MagVenture, Farum, Denmark) via a Cool-DB80 stimulation coil. The coil vertex was placed over the DMPFC under MRI guidance using the Visor 2.0 system (Advanced Neuro Technologies, Enschede, The Netherlands). The details of MRI acquisition, neuronavigation, and motor threshold procedures are described in Supplement 1. Stimulation was delivered at 120% of resting motor threshold, at 10 Hz, with a duty cycle of 5 seconds on and 10 seconds off, for a total of 3000 pulses in 60 trains per hemisphere per session. Preferential stimulation of each hemisphere was accomplished by lateral coil orientation (36,37) (Figure 1A).

Clinical Assessments

In the week before treatment, before motor threshold testing, patients underwent a baseline clinical assessment incorporating the HAMD-17 as the primary outcome measure (38). Patients also completed a battery of self-report BDI-II (39), Beck Anxiety Inventory (40), 16-item self-rated Quick Inventory of Depressive Symptomatology (QIDS) (41), Sheehan Disability Scale (42), Quality of Life Enjoyment and Satisfaction Questionnaire (43), and Warwick-Edinburgh Mental Well-Being Scale (44). This set of clinician-rated and self-report assessments was repeated after each five sessions of treatment, with follow-up assessments scheduled 2, 4, 6, 12, and 26 weeks posttreatment. The Clinical Global Impression of severity was also obtained before and after treatment and the Clinical Global Impression-Improvement measure was collected posttreatment.

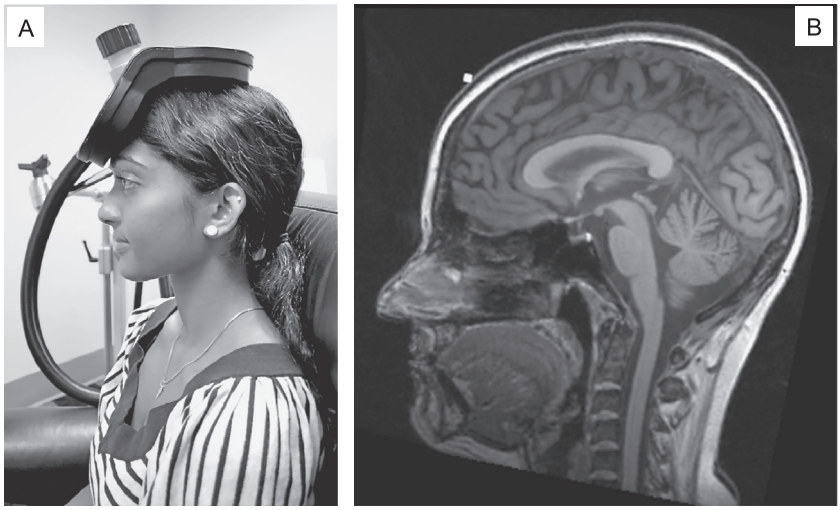

Figure 1. (A) Demonstration of placement of repetitive transcranial magnetic stimulation coil for dorsomedial prefrontal cortex stimulation with orientation of current flow to achieve preferential stimulation of the left hemisphere. In this series, 3000 pulses of 10 Hz stimulation at 120% resting motor threshold were applied to left then right hemisphere at each session. **(B)** T1 anatomical magnetic resonance imaging scan with small white square indicating the positioning of the coil vertex in a representative subject. To achieve dorsomedial prefrontal cortex coverage, the coil was placed at a scalp location corresponding to the Talairach coordinate (x 0, y +60, z +60), corresponding to ~25% of the nasion-inion distance.

Functional Neuroimaging Analysis

Resting-state functional neuroimaging data were preprocessed using the FSL platform (45); six-regressor motion correction was performed, and the CompCor package was applied to correct for white matter and cerebrospinal fluid noise sources (46). Differences in network activity among patients were then assessed using a graph-theoretical approach. The approach is described in greater detail in Supplement 1. To summarize, we first applied the resting-state connectivity-based atlas of Craddock *et al.* (47) to each preprocessed fMRI series to define a set of 516 nodes, or regions of interest (ROI), in the cortical and subcortical gray matter. The time course of activity for each ROI was extracted and used to generate a whole-brain cross-correlation matrix (Pearson's *r*). The Ledoit-Wolf shrinkage estimate was then used to generate a partial correlation matrix (48,49), which was transformed to an adjacency matrix with a sparsity of .1. This value achieved maximum graph modularity, while at the same time avoiding fragmentation of the graph into multiple subcomponents (detailed methods in Supplement 1). This adjacency matrix was then used to calculate a betweenness centrality measure for each node using the MATLAB BGL toolbox (MathWorks, Natick, Massachusetts) (Supplement 1). These values were then used to generate a normalized map of whole-brain BC values for each subject. These maps were used as the basis of between-subject comparisons, with significance testing via a 100,000-iteration Monte Carlo approach, to identify ROIs showing significant baseline differences in BC between treatment responders versus nonresponders.

Results

Clinical Outcomes

Clinical outcomes are summarized in Table 1. On the primary outcome measure, HAMD-17, 24 of 47 patients (51.1%) achieved a ≥50% reduction in symptoms and 20 of 47 patients (42.6%) achieved the remission criterion of HAMD-17 ≤7 posttreatment. On the secondary measure (BDI-II), outcomes were similar, with 23 of 47 patients (48.9%) reporting a ≥50% reduction in symptoms and 21 of 47 patients (44.7%) achieving the remission criterion of BDI -II ≤12 posttreatment. On continuous measures, the group as a whole improved from 22.9 ± SD 7.0 before treatment to 11.8 ± SD 9.3 posttreatment on the HAMD-17 ($p < .001$) and 32.8 ± SD 10.7 to 19.9 ± SD 15.2 on the BDI-II ($p < .001$) (Table 1). Symptomatic improvement proceeded approximately linearly, week by week during treatment (Figure S1 in Supplement 1).

Closer examination of the degree of improvement across individuals, via kernel density estimation, revealed a bimodal response distribution (Figure 2). Specifically, the probability distribution function contained two peaks or subpopulations: one with relatively little response to treatment (peak, 18% improvement) and another subpopulation with a much more robust response (peak, 84% improvement). The local minimum of the probability distribution function between these two groups lay at 48% improvement on HAMD-17, suggesting that the use of a 50% response criterion did indeed provide an appropriate segmentation between two distinct subpopulations and not an arbitrary threshold on a single unimodal distribution of response.

Given the presence of a bimodal distribution of outcomes, additional separate analyses were carried out for responders and nonresponders to quantify the degree and time course of response among each group (Table 1). Among responders, scores improved from 21.4 ± SD 6.7 pretreatment to 4.5 ± SD 3.8 posttreatment on the HAMD-17 and 27.8 ± SD 7.9 to 9.5 ± SD 7.2 on the BDI-II, representing a mean improvement from the moderate to the remitted range of symptom severity (Table 1, Figure 3).

Clinical Predictors of Outcome

To identify features of the clinical presentation that might be predictive of outcome, baseline demographic, patient history, and symptom scale measures were correlated to percentage improvement in HAMD-17 scores from pretreatment to posttreatment.

None of the seven electroconvulsive therapy refractory cases achieved either response or remission on either the HAMD-17 or the BDI-II. There was no significant correlation between percentage improvement in HAMD-17 score and duration of current episode ($r = -.18$; $p = .12$), number of previous medication trials ($r = -.02$; $p = .44$), age ($r = .03$; $p = .41$), or gender ($r = .11$; $p = .23$). Nor was there any significant difference in percent HAMD-17 improvement between patients with unipolar or bipolar illness ($t_{45} = .05$; $p = .96$). Two of 2 patients with bipolar disorder, type I, and 1 of 7 patients with bipolar disorder, type II, met HAMD-17 response criteria.

Table 1. Treatment Outcomes Overall and in Subgroups

	Pretreatment		Posttreatment		
	Mean	SD	Mean	SD	*p*
Overall ($n = 47$)					
HAMD-17	22.9	7.0	11.8	9.3	<.001
BDI-II	32.8	10.7	19.9	15.2	<.001
BAI	21.3	14.6	13.2	14.4	<.001
CGI	4.8	1.1	2.4	1.9	<.001
SDS-Work	7.9	2.3	6.0	3.5	<.001
SDS-Social	7.6	2.3	5.2	3.1	<.001
SDS-Family	7.0	2.2	4.9	3.0	<.001
SDS-Days Lost	3.5	2.8	2.6	3.0	.055
SDS-Days Unproductive	5.2	2.2	3.7	3.0	.003
WEMWBS	29.9	5.7	39.2	12.4	<.001
QLESQ	32.5	6.4	41.1	12.1	<.001
Responders ($n = 24$)					
HAMD-17	21.4	6.7	4.5	3.8	<.001
BDI-II	27.8	7.9	9.5	7.2	<.001
BAI	16.9	12.3	10.7	11.3	.001
CGI	4.4	.9	1.2	0.6	<.001
SDS-Work	7.1	2.5	4.3	3.5	<.001
SDS-Social	7.0	2.5	3.9	2.9	<.001
SDS-Family	6.3	2.5	3.6	2.9	<.001
SDS-Days Lost	3.5	3.1	1.4	2.6	.002
SDS-Days Unproductive	5.2	2.1	2.3	2.7	<.001
WEMWBS	32.2	4.9	46.8	9.3	<.001
QLESQ	34.5	6.0	48.7	9.6	<.001
Nonresponders ($n = 23$)					
HAMD-17	24.5	7.1	19.4	6.8	<.001
BDI-II	37.9	10.9	30.7	13.8	<.001
BAI	25.9	15.6	15.9	17.0	<.001
CGI	5.5	1.3	4.0	1.9	.037
SDS-Work	8.8	1.7	7.6	2.8	.055
SDS-Social	8.1	2.0	6.7	2.7	.037
SDS-Family	7.7	1.6	6.5	2.2	.017
SDS-Days Lost	3.5	2.5	3.9	2.9	.239
SDS-Days Unproductive	5.2	2.3	5.4	2.3	.687
WEMWBS	27.4	5.6	30.5	9.3	.014
QLESQ	30.3	6.2	32.9	8.9	.157

BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-II; CGI, Clinical Global Impression; HAMD-17, Hamilton Depression Rating Scale, 17 item; QLESQ, Quality of Life Enjoyment and Satisfaction Questionnaire; SDS, Sheehan Disability Scale; WEMWBS, Warwick-Edinburgh Mental Well-Being Scale.

To identify any specific symptoms that might predict outcome, we then correlated HAMD-17 improvement to each of 115 individual items from the entire set of baseline symptom scales (Table 2; Table S1 in Supplement 1). Following Bonferroni correction for multiple comparisons ($p < 4.35 \times 10^{-4}$), there were three items that emerged as significantly, negatively predictive of HAMD-17 improvement: BDI-II item 2–pessimism ($r = -.52$; $p = 6.47 \times 10^{-5}$), BDI-II item 4–loss of pleasure ($r = -.49$, $p = 1.98 \times 10^{-4}$), and QIDS item 1–general interest ($r = -.47$; $p = 3.82 \times 10^{-4}$). The correlation between percent HAMD-17 improvement and the normalized composite product of these measures was $r = -.61$ ($p = 1.29 \times 10^{-6}$) (Figure 3B).

No individual items on HAMD-17, Quality of Life Enjoyment and Satisfaction Questionnaire, or Warwick-Edinburgh Mental Well-Being Scale significantly predicted outcome. Likewise, at the Bonferroni-adjusted threshold, there was no significant predictive correlation to outcome for overall baseline score on the BDI-II ($r = -.42$; $p =$ ns), HAMD-17 ($r = -.20$; $p =$ ns), or QIDS ($r = -.45$; $p =$ ns) (Table 2; Table S1 in Supplement 1).

Neuroimaging Predictors of Outcome

As a preliminary, first-pass assessment of the physiological relevance of the BC-mapping approach, we identified the set of regions in the upper fifth percentile (two-tailed) of BC difference between responders and nonresponders (Table S2 and Figures S2 and S3 in Supplement 1). This set of regions corresponded well to the network of regions previously implicated in depression and emotional reappraisal (12,14,50,51). Specifically, responders showed significantly higher BC than nonresponders in right amygdala, ventral striatum, temporal pole, and DMPFC, as well as a region in left DLPFC and anterior insula. Nonresponders showed significantly higher BC than responders in left VMPFC, as well as regions in left DLPFC, DMPFC, dorsal ACC, retrosplenial cingulate cortex, and right anterior insula. Thus, the BC approach did appear successful in localizing predictive differences to a set of regions with plausible involvement in emotion regulation. (Figure 4B).

We next applied to this map a more stringent threshold, Bonferroni-corrected for multiple comparisons as with the clinical measures, across the 516 regions of interest. At this threshold, only the node in left VMPFC at Montreal Neurological Institute coordinate (x −4, y 48, z −15) showed markedly higher BC in nonresponders than in responders to treatment ($p = .00001$). This result was robust across a range of graph sparsities from .1 to .5, assessed in increments of .02, suggesting a relative lack of contingency on the choice of connectivity threshold (Figure S6 in Supplement 1). Of note, this specific VMPFC region corresponded very closely to the VMPFC region previously identified in neuroimaging meta-analyses as activated for a wide variety of rewarding stimuli in healthy control subjects (52,53) (Figure 4B).

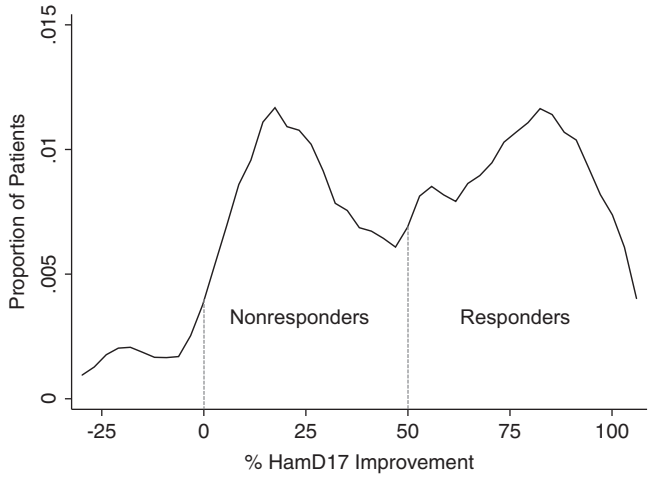

Figure 2. Probability distribution function for percent 17-item Hamilton Rating Scale for Depression (HAMD-17) improvement from pretreatment to posttreatment across the 47 patients in the series. The degree of response was not unimodal but instead followed a sharply bimodal distribution with a nonresponder group showing ~15% to 25% improvement and a responder group showing ~80% to 90% improvement in symptoms. The local minimum of the probability distribution lay almost exactly at 50% improvement, suggesting that the original patient sample of medication-resistant major depressive episode patients was appropriately partitioned by the conventional 50% improvement criterion into distinct dorsomedial prefrontal cortex-repetitive transcranial magnetic stimulation responder and nonresponder subpopulations.

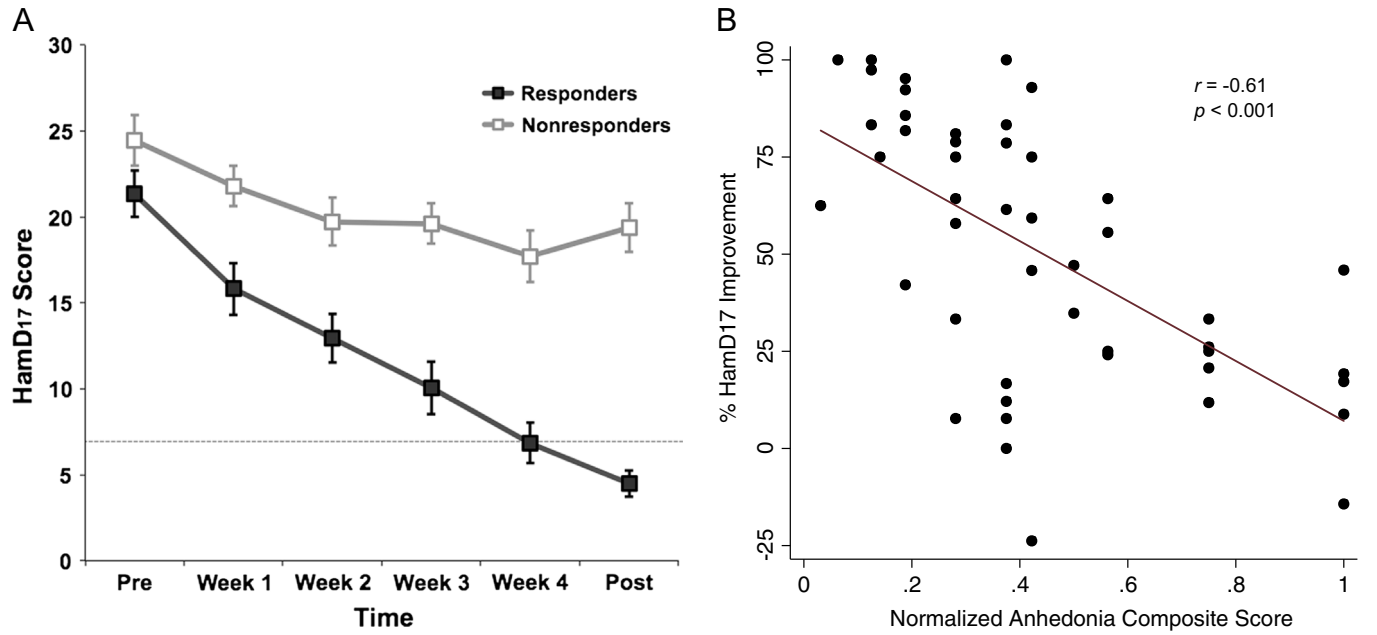

Figure 3. (A) Trajectories of improvement in responder and nonresponder subpopulations. Responders showed a steady improvement to meet the remission criterion of 17-item Hamilton Rating Scale for Depression (HAMD-17) score ≤7 over the course of treatment, while nonresponders showed minimal improvement. **(B)** The normalized product of pretreatment scores on three anhedonia-related items (Beck Depression Inventory-II item 2, Beck Depression Inventory-II item 4, and Quick Inventory of Depressive Symptomatology item 13) was a strong negative predictor of percentage improvement in HAMD-17 score from pretreatment to posttreatment.

Finally, to better compare the network connectivity profile of this region in responders and nonresponders, we performed a statistical comparison of the whole-brain resting-state connectivity of this left VMPFC region with the other 515 regions across the two groups (whole-brain false discovery rate-corrected $p < .05$) (Table 3, Figure 4C,D). Compared with responders, nonresponders showed significantly lower connectivity to left VMPFC in the ventral tegmental area and left caudate nucleus. They also showed lower significant connectivity to left VMPFC in a left-lateralized set of cortical regions that included the left DMPFC, DLPFC, inferior parietal lobule, and anterior insula. In addition, compared with responders, nonresponders showed higher connectivity to left VMPFC in a corresponding right-lateralized set of cortical regions that included right DMPFC and DLPFC, as well as right frontopolar cortex and posterior cingulate cortex (Table 3, Figure 4C,D).

Table 2. Clinical Predictors of Outcome

Symptom Scale	Item	Correlation to % HAMD-17 Improvement	*p*
BDI-II	Pessimism	−.520	6.47×10^{-5}
	Loss of pleasure	−.488	1.98×10^{-4}
QIDS	General interest	−.468	3.82×10^{-4}
Other	QIDS - Total	−.448	ns
	HAMD-17 - Total	−.204	ns
	Age	.033	ns
	Gender	−.110	ns
	Episode duration	−.177	ns
	# Failed medicine trials	−.022	ns
	Unipolar/bipolar	−.007	ns

All significantly predictive items were identified using a threshold $p < .05$, Bonferroni-corrected for multiple comparisons across the 115 items surveyed in the baseline mood and functional scales (i.e., threshold $p = 4.35 \times 10^{-4}$).

HAMD-17, Hamilton Depression Rating Scale, 17 item; BDI-II, Beck Depression Inventory-II; ns, nonsignificant; QIDS, Quick Inventory of Depressive Symptomatology–Self-rated 16-item scale.

Discussion

To our knowledge, this is the first report on either the effectiveness or predictors of outcome for DMPFC-rTMS in a series of patients with a medication-resistant major depressive episode. The results of the present study suggest that the patients did not respond uniformly to treatment but instead showed a strongly bimodal separation into a responder and a nonresponder group (Figure 2). The implication is that the original sample of patients, though all meeting criteria for a major depressive episode, may have comprised at least two distinct subgroups rather than a uniform and homogeneous population. Of note, a similar bimodal heterogeneity of response has recently been described in meta-analyses of clinical trials for duloxetine (54) and escitalopram (55).

Examination of the pretreatment clinical symptomatology confirmed a set of predictive differences between eventual responders and nonresponders at a high level of significance. The predictive items concurred across two independent scales (BDI-II and QIDS) and could potentially represent pathology of the appetitive and consummatory aspects of reward: pessimism (appetitive), general interest in formerly enjoyed activities (appetitive), and loss of pleasure (consummatory). The former two symptoms, in combination, have been observed elsewhere to be associated in major depression (56).

More strikingly, the neuroimaging results were congruent with the clinical predictors in identifying a single, specific VMPFC

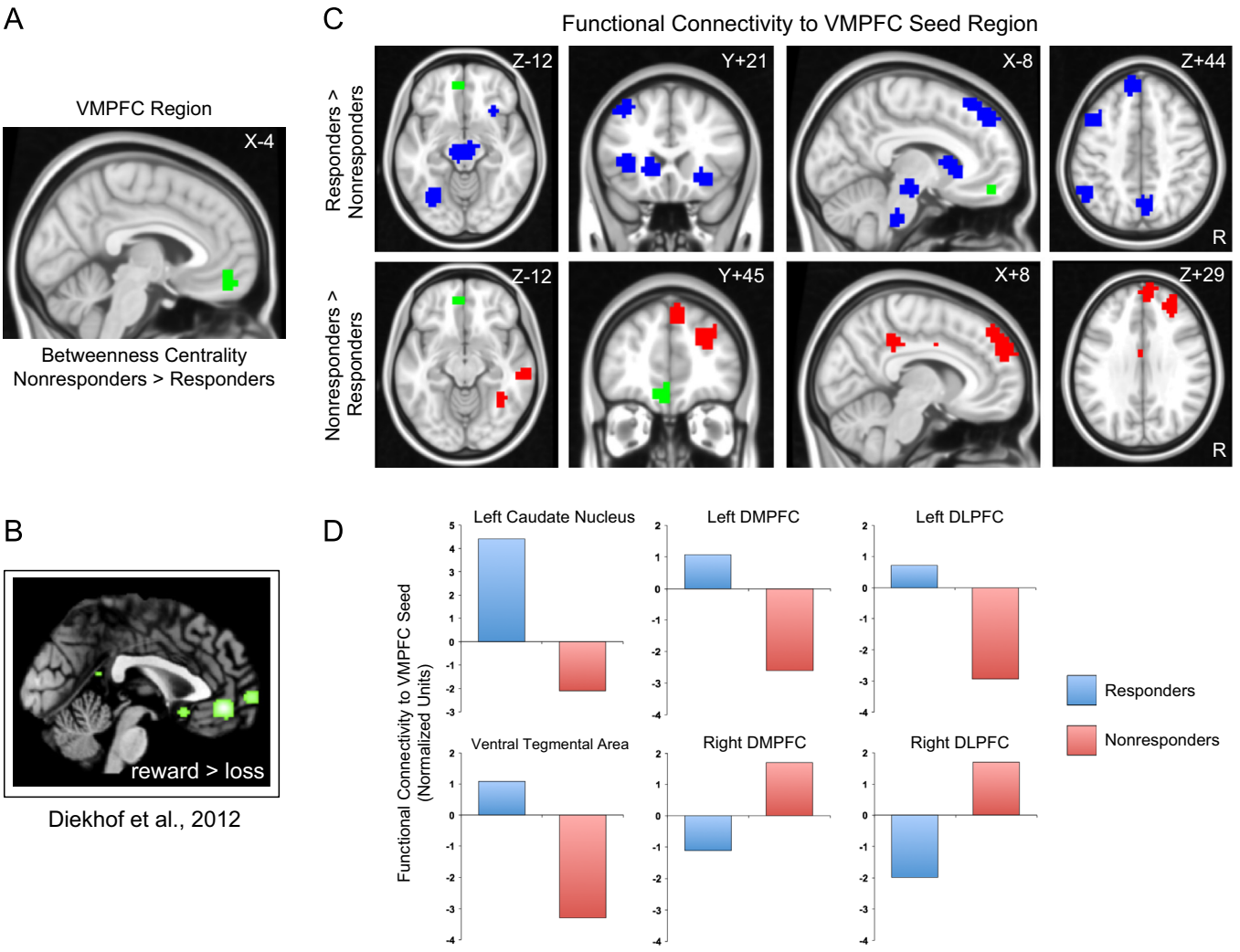

Figure 4. Neuroimaging correlates of response to dorsomedial prefrontal cortex (DMPFC)-repetitive transcranial magnetic stimulation. A comparison of betweenness centrality values in nonresponders versus responders to treatment revealed a single region whose betweenness centrality was significantly higher in nonresponders **(A)**. This region lay in left ventromedial prefrontal cortex (VMPFC), at a location similar to that observed in previous meta-analyses of reward- versus loss-related activation in healthy control subjects **(B)** [reprinted from Diekhof *et al.* (53) with permission from Elsevier, copyright 2012]. Compared with responders, nonresponders showed significantly lower functional connectivity between the VMPFC seed and the ventral tegmental area and striatum, as well as between the VMPFC seed and a left-lateralized network of cortical regions including left DMPFC, dorsolateral prefrontal cortex (DLPFC), and anterior insula **(C,D)**. Conversely, nonresponders showed significantly higher functional connectivity from the VMPFC seed to a right-lateralized network of cortical regions including right DMPFC, DLPFC, and posterior cingulate cortex.

region, previously shown to activate consistently for rewarding stimuli across a wide variety of studies, as predictive of treatment outcome. This region showed higher BC in nonresponders, and thus could potentially be considered as a bottleneck region in depressed patients with anhedonia and nonresponsiveness to dorsomedial stimulation. In nonresponders, this region showed significantly lower connectivity to a circuit of dopaminergic regions, including the ventral tegmental area and left caudate nucleus, suggesting a disruption of the reward pathway, which would be in keeping with the clinical features of this subpopulation.

There was also a striking hemispheric asymmetry in the set of brain regions showing connectivity to the left VMPFC seed in responders versus nonresponders. Nonresponders had significantly higher functional connectivity to left VMPFC from a set of right-lateralized regions, including right DMPFC, DLPFC, frontopolar cortex, posterior cingulate cortex, and middle temporal gyrus. In contrast, they showed significantly lower functional connectivity to left VMPFC from a similar but left-lateralized set of regions including left DMPFC, DLPFC, caudate nucleus, inferior parietal lobule, and occipital cortex. We also note a left-hemispheric lateralization of the VMPFC seed region itself, in contrast to the bilateral reward-related activity seen in studies in healthy control subjects (52,53).

The distinct and opposite lateralized pattern of left VMPFC connectivity in responders versus nonresponders was rather striking and bears further consideration. On one view, a deficit in left hemisphere connectivity to ventral prefrontal regions in nonresponders could be considered consistent with the original rationale for targeting left DLPFC in the first studies of excitatory rTMS for major depression (57,58) to address hypoactivity of left prefrontal regions. This perspective would suggest the possibility of achieving further gains in rTMS efficacy by tailoring the laterality and frequency of rTMS to the individual patient based

Table 3. Regions with Higher Significant Pretreatment Functional Connectivity to the Identified VMPFC Region in Responders Versus Nonresponders

Region	Brodmann Area	MNI Coordinates			Significance	
		x	y	z	*Z*	*p*
L VMPFC Connectivity: Responders > nonresponders						
L caudate nucleus	–	−14	20	0	6.51	7.63×10^{-11}
	–	−14	14	9	2.75	3.00×10^{-3}
Ventral tegmental area	–	−1	−26	−6	5.63	9.22×10^{-9}
	–	6	−18	−13	4.38	5.81×10^{-6}
	–	−8	−19	−13	3.73	9.47×10^{-5}
Pons	–	−6	−28	−39	5.21	9.68×10^{-8}
	–	3	−22	−33	2.59	4.82×10^{-3}
L dorsomedial prefrontal cortex	8	−11	32	56	3.66	1.24×10^{-4}
		−9	45	46	3.21	6.64×10^{-4}
L dorsolateral prefrontal cortex	9	−44	13	45	3.65	1.31×10^{-4}
	9	−37	20	52	3.52	2.14×10^{-4}
L occipital cortex	19	−31	−66	−13	3.49	2.44×10^{-4}
L inferior parietal lobule	39/40	−50	−54	44	3.36	3.92×10^{-4}
	39/40	−56	−52	33	2.80	2.55×10^{-3}
	40	−39	−47	55	2.81	2.51×10^{-3}
L cerebellum	–	−38	−43	−33	3.33	4.27×10^{-4}
L anterior insula	–	−35	25	5	3.13	8.77×10^{-4}
R occipital cortex	18	31	−88	4	4.25	1.09×10^{-5}
R anterior insula	–	29	21	−6	3.58	1.73×10^{-4}
R precuneus	7	4	−65	40	3.18	7.25×10^{-4}
L VMPFC Connectivity: Nonresponders > responders						
R fusiform gyrus	37	35	−52	−17	3.99	3.31×10^{-5}
R dorsolateral prefrontal cortex	9	28	33	36	3.69	1.13×10^{-4}
	46	29	45	28	3.26	5.57×10^{-4}
	6	40	−1	53	2.91	1.81×10^{-3}
R posterior cingulate cortex	23	5	−39	39	3.11	9.20×10^{-4}
R middle temporal gyrus	20	61	−26	−12	3.08	1.02×10^{-3}
R dorsomedial prefrontal cortex	9	7	50	42	2.96	1.55×10^{-3}
	9	6	58	30	2.81	2.49×10^{-3}
R frontopolar cortex	10	19	67	9	2.91	1.82×10^{-3}
L middle cingulate cortex	24	−2	−3	34	4.25	1.08×10^{-5}
L middle paracingulate cortex	32	−7	12	42	3.36	3.86×10^{-4}

All activations were identified using a threshold $p < .05$, Bonferroni-corrected for multiple comparisons across the 515 cross-correlations performed between the VMPFC region and each other region of interest in the atlas (i.e., threshold $p = 9.67 \times 10^{-5}$). Images of identified regions are presented in Figure 4B.

L, left; MNI, Montreal Neurological Institute; R, right; VMPFC, ventromedial prefrontal cortex.

on the lateralization of whole-brain functional connectivity to VMPFC or other associated regions such as the amygdala. Alternatively, the observed pattern of lateralization could potentially reflect the larger proportion of female subjects in the present study: previous studies have identified a gender-dependent hemispheric asymmetry in which female subjects preferentially activate left hemisphere VMPFC (as well as amygdala, hippocampus, and ACC) in response to negative stimuli, while male subjects preferentially activate these regions for positive stimuli (59,60). In addition, previous observations of left- and right-hemisphere specialization for control of the parasympathetic and sympathetic nervous systems, respectively, may also be of relevance in interpreting the lateralized results observed in the present study (61).

The lack of response to treatment among a subgroup of patients in the present study could also potentially reflect the deep anatomical location of the VMPFC region, beyond the reach of the field applied during DMPFC-rTMS. This hypothesis generates three testable predictions: stimulation of the VMPFC region should also be effective in a subgroup of depressed patients; this subgroup should be characterized by prominent anhedonic symptoms before treatment; and these anhedonic symptoms should improve with stimulation.

While rTMS has not yet been applied to the VMPFC in this setting, two independent groups have targeted this pathway in depression using DBS, applied either to the subgenual ACC (62,63) or the nucleus accumbens (64). In both cases, neuroimaging investigations revealed DBS to deactivate precisely the VMPFC region identified in the present study (63,64). With DBS of the nucleus accumbens, hedonic response improved significantly overall, and responders showed long-term improvements in pursuit of positive activities (65). With DBS of the subgenual ACC, higher baseline symptoms of anhedonia predicted better, rather than poorer, treatment response—the opposite pattern from dorsomedial stimulation based on the results of the present study (66).

In the context of previous neuroimaging studies suggesting dorsomedial hypoactivity and ventromedial hyperactivity in major depression (12,67), the results of this study and the results of the DBS studies suggest that there may exist at least two distinct

depression subtypes: a dorsal-hypoactive type, responsive to DMPFC-rTMS and characterized by preserved hedonic response, and a ventral-hyperactive type, responsive to DBS of VMPFC reward pathways and characterized by disrupted hedonic response. This hypothesis would be consistent with the lesion and volumetric literature associating vulnerability to depression with injury/gray matter reduction in DMPFC and protective effects against depression with injury/gray matter reduction in VMPFC (22,24).

A significant limitation of the present study involves the use of an open-label design without sham stimulation. Such a design cannot precisely quantify the specific versus the nonspecific effects of treatment suing DMPFC-rTMS. For context, it should be kept in mind that a recent meta-analysis quantified the response and remission rates for sham DLPFC-rTMS at only 10% and ~5%, respectively, with the response and remission rates for active DLPFC-rTMS at 29.3% and 18.6%, respectively (68). Thus, it would be difficult to account for the present study's observed response and remission rates of 51% and 43%, respectively, as due entirely to sham effects. However, a randomized, sham-controlled trial of DMPFC-rTMS will be an essential follow-up to the present open-label case series in establishing the effectiveness of this stimulation target. A blinded comparison of the efficacy of DMPFC-rTMS and DLPFC-rTMS might also be worth pursuing in the future.

Other significant limitations include the use of a relatively small sample size and the availability of functional neuroimaging in only a subset of patients. This leaves open the possibility that additional significant predictors of outcome might reveal themselves in a larger or a more standardized sample. For example, the considerable heterogeneity of medication classes and doses in this sample precluded any determination of whether medication type or dose might be predictive of outcome, and this remains an open question for more systematic study in the future.

The present study also does not clarify whether hedonic response and reward-circuit integrity are also distinguishing features for responders versus nonresponders to rTMS of the conventional target, DLPFC. Symptoms of apathy have been reported to predict nonresponse to DLPFC-rTMS using a deep stimulation coil, suggesting the possibility of such a relationship (69). The generalizability of the present results to DLPFC-rTMS remains an important question for further study.

In conclusion, the search for clinically meaningful subtypes of major depression is now beginning to profit from recent advances in understanding major depression as a network-level pathology of connectivity among emotion-regulating regions of the brain. Anatomically targeted therapies, such as rTMS and DBS, may be particularly well-suited to individualized treatment based on clinical presentation. Stimulation studies now appear to be consistent with lesion studies in identifying DMPFC and VMPFC as playing central, yet complementary, roles in the pathophysiology of depression. Further studies comparing the effects of stimulation at these two sites, in individual patients, will clarify whether this distinction is robust and clinically meaningful. If so, the long-recognized core depression symptom of anhedonia, and its underlying neural correlates, may prove themselves to be reliable guides for maximizing the likelihood of successful treatment in patients with otherwise intractable illness.

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